AD_____

Award Number: DAMD17-98-1-8650

TITLE: Ovarian Cancer Prevention Program

PRINCIPAL INVESTIGATOR: Paul F. Engstrom, M.D.

CONTRACTING ORGANIZATION: Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

REPORT DATE: October 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2001	Annual (30 Sep 00 - 29 Sep 01)

4. TITLE AND SUBTITLE
Ovarian Cancer Prevention Program

5. FUNDING NUMBERS
DAMD17-98-1-8650

6. AUTHOR(S)
Paul F. Engstrom, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

E-Mail: **PF_Engstrom@fccc.edu**

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Report contains color.

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

The goals of this research are to develop interdisciplinary studies of the etiology, biology and prevention of ovarian cancer. **Project I, Ovarian Cancer Consortium** has registered 687 participants including 234 patients representing 320 families. The Core Laboratory has collected, processed and banked biospecimens from 496 subjects. **Project II, Facilitating Decision Marking About Prophylactic Oophorectomy**: baseline data on 80 women are available for preliminary analysis; 15 women, (19%) made a decision about having prophylactic oophorectomy while 66 women (76%) have not made a decision, and 4 women (5%) did not answer the questionnaire. Fifteen women said they would likely have a prophylactic oophorectomy in the near future. **Project III, Phase II Chemoprevention Study of Ovarian Cancer**: this placebo-controlled randomized protocol using 4HPR has been written, approved by the Dept. of Defense, the National Cancer Institute Chemoprevention Branch, and the FDA. The Gynecologic Oncology Group has implemented the study throughout the country for interested gynecologic oncologists. Data entry and quality control systems have been established and 14 different case report forms are finalized. Seven women have signed consent forms, 6 were enrolled in the Ovarian Tissue Donation Portion of the study, and one has randomized to treatment and completed her prophylactic oophorectomy in March 2000.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Ovarian, Cancer, Prevention	40
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

Front Cover 1

Standard Form SF 298 2

Table of Contents 3

Project I
Introduction 5
Body 5
Key Accomplishments 7
Reportable Outcomes 8
Conclusions 8

Project II
Introduction 10
Body 10
Key Accomplishments 11
Reportable Outcomes 11
Conclusions 12
References 13

Project III
Introduction 15
Body 15
Key Accomplishments 16
Reportable Outcomes 17
Conclusions 20

Laboratory Core
Introduction 26
Body 26
Key Accomplishments 29
Reportable Outcomes 30
Conclusions 30

Data Management Core
Introduction 32
Body 32
Key Accomplishments 33
Reportable Outcomes 33
Conclusions 34

Appendices 36

ANNUAL REPORT – YEAR THREE

PROJECT I

OVARIAN CANCER CONSORTIUM FOR RESEARCH AND SURVEILLANCE (OCCRS)

Project Director	**Mary B. Daly, M.D., Ph.D.**	**Fox Chase Cancer Center**
Co-Investigator	**Andrew K. Godwin, Ph.D.**	**Fox Chase Cancer Center**
Statistician	**Andre Rogatko, Ph.D.**	**Fox Chase Cancer Center**

INTRODUCTION

Ovarian cancer continues to pose a significant threat to mortality in the 25,000 women estimated to develop the disease in the United States in 2001. The search for a clearer understanding of the causes of the disease as well as how to prevent and detect it is underway through research efforts such as the Ovarian Cancer Consortium for Research and Surveillance (OCCRS). The OCCRS, now in operation at Fox Chase Cancer Center for three years has had a steady base of recruitment through established networking procedures both internally and with three collaborating institutions. Current enrollment of 687 participants includes 234 ovarian cancer patients and 453 high risk women representing 320 families from 42 states and Canada. While continuing to enlist new individuals into the OCCRS, staff has focused on the recruitment of extended family members and the procurement of medical records, blood samples and tumor tissue specimens. The relational database system is constantly updated to include incoming information. Laboratory research continues as directed by Dr. Andrew Godwin. Significant progress has been made in the Symptom Checklist Project. We are encouraged by the growing community support for ovarian cancer research and advocacy.

BODY

Established procedures for recruitment of participants and collection of data and biospecimens allowed for increased activity in the OCCRS during year three. The following is a description of the research accomplishments associated with each Task as outline in the approved Statement of Work.

Task 1. Development and Implementation of a Recruitment Strategy

Key personnel actively involved at each site are listed in **Appendix A**. The collaborative sites encountered a variety of logistical issues that curtailed the numbers of women recruited into the study at those sites. Such issues, which should be considered when designing future joint research efforts, included changes in staff committed to the project, and extended length of time required to operationalize recruitment procedures (due to IRB processes and development to population-specific marketing and networking strategies). Also it has been noted that ovarian cancer patients, while often motivated to help research, may be dealing with treatment-related issues that can compromise follow-through with study requirements.

Reading Medical Center: The PI and his colleague, both gynecological oncologists, left their practice at this site during the past year and the transition may have impacted referral to the Family Risk Assessment Program (FRAP). The FRAP coordinator holds breast and ovarian cancer education sessions on an every other month basis and while attendance at these sessions is steady, the women do not regularly pursue participation in research studies.

Wake Forest University Baptist Medical Center: Recruitment of probands has been steady but a challenge has been encountered in having extended family members provide paperwork and blood donation. Blood collection kits are mailed to family members who live in a wide geographic area; it is their responsibility to have the samples drawn and shipped. The process could impose a burden to some persons who may not share the same commitment to research as their family members. The project coordinator notes a lengthy period of time to

establish procedures for release of tumor samples from the pathology department. A fee is charged for all samples released, even within the institution.

Cooper Medical Center: Having only been up and running for a little over one year, the program at Cooper was quite successful. Networking with a local gynecologic oncology practice was productive for referrals. The project coordinator notes more interest in the OCCRS on the part of ovarian cancer patients as opposed to the high risk women identified through their Cancer Risk Evaluation Program. A challenge in having extended family members comply with study requirements was encountered, similar to the experience at Wake Forest.

Total Participation from all sites (including FCCC):

To date, 687 participants, including 234 patients and 453 high risk women, representing 320 families are enrolled. These numbers reflect persons who have agreed to participate and do not include deceased relatives on whom we have collected proxy information. Of these families, six are from Reading, 31 from Wake Forest and 18 from Cooper. Two hundred thirty-one (231) families had one case of ovarian cancer, 52 had two cases and 21 had more than two. One hundred seventy-four (174) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with *BRCA1* and *BRCA2* mutations. The median age of OCCRS participants is 48 years, with a range of 16 to 93 years. Participants live in 42 states and Canada.

Task 2. Establishment of a Computerized Data Base

The relational database system in place last year continues to maintain all information obtained in this research. Health history, family history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data are continually added to the system and annual follow-up data is collected from all participants as per standard FRAP protocol. Multigenerational pedigrees are generated for all probands.

Task 3. Development of Informed Consent Practice

Ongoing review for the OCCRS (FCCC protocol # 98-820) was performed by the IRB on 8/7/01. Reapproval of the Symptom Checklist substudy was incorporated into the ongoing review for the OCCRS. Informed consent is obtained from all participants as part of recruitment into the study.

Task 4. Establish an Ovarian Cancer Tissue Bank

Biospecimen collection continues via established procedures. As noted earlier it has been a challenge to encourage extended family members to return blood sample kits. To date, the Core laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 469 blood samples. Four hundred and five (405) samples were collected through FCCC, 38 through Wake Forest, 9 through Reading and 17 from Cooper.

Additionally, 81 sets of tumor tissue blocks and/or slides have been released to FCCC from various pathology departments in hospitals where OCCRS participants had surgery. Wake Forest samples are expected to be forwarded to FCCC in the near future.

Task 5. Development and Implementation of Symptom Checklist

The goal of interviewing 50 newly diagnosed patients has been met with 52 interviews completed, either in person or over the telephone. After obtaining informed consent, the interviews are recorded and transcribed. Analysis to extract the experience of particular symptoms, their duration prior to diagnosis and which symptoms prompted the women to seek medical evaluation is in the beginning stages. Development of the checklist tool will be undertaken after the interview analysis is completed.

Task 6. Standardization of Genetic Risk Counseling Protocols

The comprehensive genetic risk counseling protocol developed in the Margaret Dyson Family Risk Assessment Program at FCCC is the model for the programs at the Reading Medical and Cooper Medical Centers. The Wake Forest site collaborates with a certified genetic counselor to provide risk counseling.

Task 7. Develop a Comprehensive Education Program for Providers and Participants

We continue to use a sophisticated compact disc-interactive (CD-i) format for educational purposes, alerting women at risk to the genetic basis, screening and prevention of ovarian cancer. This format is complemented by a personal binder of information provided to each participant, to serve as a reference and enhance the cancer risk counseling process.

All participants in FRAP receive a periodic newsletter, *Prevention Matters,* with an insert devoted to ovarian cancer research and education (**See Appendix B**).

The FCCC website, http://www.fccc.edu is updated on a regular basis and includes institution-specific information on ovarian cancer treatment and risk assessment. The site links to comprehensive ovarian cancer educational information through the Cancer Information Service.

On an annual basis the project manager participates in a local advocacy walk, the National Ovarian Cancer Coalition's "Walk for the Whisper" to raise awareness. Educational materials are shared with the public regarding screening, prevention and risk assessment for ovarian cancer.

In late October 2001 we will display four ovarian cancer awareness quilts in our Cancer Prevention Pavilion lobby to promote increased understanding of issues related to ovarian cancer. We also are designing a FCCC ovarian cancer awareness quilt that will be made by patients, family members and staff.

KEY RESEARCH ACCOMPLISHMENTS

- Obtained and banked 469 blood samples into the OCCRS during the course of the grant
- Distributed DNA from blood and ovarian tumors to multiple investigators for various studies
- Collected 37 overtly normal ovaries from women undergoing oophorectomies. Two (2) of these individuals had participated in the 4-HPR chemoprevention trial.
- Identified 36 germline mutations in the OCCRS participants

REPORTABLE OUTCOMES

Data will be analyzed during the next year's unfunded extension.

CONCLUSIONS

Recruitment into the OCCRS has been steady, fueled by the growing community interest in ovarian cancer advocacy. Our numbers have not met those originally proposed, due in part to the logistical challenges encountered by our collaborating sites. Each site took at least one year to become fully operational and staff changes posed additional constraints. The compliance rate of those who did participate is high, despite the fact that many ovarian cancer patients experience recurrent disease and its challenges. The compliance rate of extended family members has been lower than that of the probands.

Now that a sizable resource has been collected we anticipate ongoing analysis of the data to provide important insight into the genetic basis of oncogenesis, epidemiology and symptoms of ovarian cancer.

ANNUAL REPORT-YEAR THREE

Project II

FACILITATING DECISION MAKING ABOUT PROPHYLACTIC OOPHORECTOMY

Project Director	**Dr. Suzanne M. Miller**	**Fox Chase Cancer Center**
Co-Investigator	**Dr. Carolyn Y. Fang**	**Fox Chase Cancer Center**

INTRODUCTION

Project II, *Facilitating Decision-Making about Prophylactic Oophorectomy,* focuses on how women with a familial risk of ovarian cancer make decisions regarding their preventative options, specifically prophylactic oophorectomy (surgical removal of healthy ovaries). The primary goal of the study is to explore the psychological factors that influence a woman's decision to undergo or forego the procedure. A secondary goal is to identify whether high monitors (who typically scan for and exaggerate cancer threats) show a different pattern of response than low monitors (who typically distract from and minimize health threats). Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of an enhanced counseling intervention.

BODY

A procedural plan was designed to ensure consistency in dealing with multiple sites. This entails identifying key personnel, developing a standardized protocol to contact potential participants, and the establishment of a computerized database for all study data. A series of meetings held between staff at FCCC and contacts at collaborating sites enabled us to systematically develop and enact this plan. The study is being conducted at Fox Chase Cancer Center, as well as at satellite sites including Cooper Health System and Reading Hospital. Four evaluation time-points include a baseline assessment with 3-, 6-, and 12-month follow-up assessments. Measures include background variables (i.e., demographics, personal health history, medical status), person variables (i.e., attentional style), process variables (i.e., the patient's level of perceived risk, perceived control, distress, values/goals, and self-regulatory coping strategies), and outcome variables (i.e., decision-making regarding prophylactic oophorectomy. Data obtained from this study will be used to develop an enhanced counseling intervention to facilitate decision-making and maximize patient adjustment. The Cognitive-Affective Processing (CAP) intervention will be designed to enable the prophylactic oophorectomy candidate to realistically anticipate scenarios that might develop, thereby providing a more informed basis for making her surgery decision and dealing with its consequences. A pilot study will be designed and conducted to provide a preliminary evaluation of the feasibility and efficacy of the CAP intervention.

At the time of this report, 82% percent (80/97) of women who gave verbal consent to participate have returned their written consent form and baseline packet of questionnaires. Eighty-six percent (68/79) of the women eligible to receive their 3-month assessment have returned their packets, while we are still waiting for 14% (11/79) of the distributed packets to be returned. Ninety-three percent (63/68) of the women eligible to receive their 6-month assessments have returned their packets, while we are still waiting for 7% (5/68) of the distributed packets to be returned. Seventy-nine percent (48/61) of the women eligible to receive their 12-month assessments have returned their packets, while we are still waiting for 21% (13/61) of the distributed packets to be returned.

KEY RESEARCH ACCOMPLISHMENTS

- Implementation of study protocol, initiation of recruitment efforts, and analysis of baseline data.

- A review and analysis of the literature on decision-making about prophylactic oophorectomy was conducted. This review paper, *Decision Making about Prophylactic Oophorectomy among At-Risk Women: Psychological Influences and Implications,* has been published in Gynecologic Oncology (Miller, Fang, Manne, Engstrom, & Daly, 1999).

- Completion of pilot studies investigating the predictors of women's intentions to undergo prophylactic oophorectomy. An empirical paper entitled *Anxiety/Uncertainty Reduction as a Motivation for Interest in Prophylactic Oophorectomy in Women with a Family History of Ovarian Cancer* has been submitted to the Journal of Women's Health (Hurley, Miller, et al., 2001). This study investigated the relation of cancer anxiety and other factors to interest in prophylactic oophorectomy in a group of women with varying degrees of familial risk for ovarian cancer.

- Another empirical paper, *The Influence of Attentional Style and Risk Perceptions on Intentions to Undergo Prophylactic Oophorectomy Among FDRs,* has been accepted for publication in *Psychology and Health* (Fang, Miller, Daly, & Hurley, *in press*). This paper illustrates the impact of monitoring attentional style and perceived risk on at-risk women's intentions to undergo prophylactic oophorectomy.

REPORTABLE OUTCOMES

To date, all of the women who have agreed to participate in this study are Caucasian. Approximately 82% of the women have at least a college degree, and 18% have completed a high school degree. The majority (78%) of the women are currently married. Seventy percent are currently employed. The mean age of participants is 42 years old (SD = 10.31 years).

At the time of this progress report, baseline data for 80 women were available for preliminary analysis. The analysis indicated that fifteen women (19%) had made a decision about having a prophylactic oophorectomy, while 61 women (76%) had not made a decision and 4 women (5%) did not answer the question. Of the 61 women who were still in the decision-making process, 18 women were quite a bit (21.3%) or definitely (8.2%) interested in learning more about prophylactic oophorectomy. Fifteen women stated that it was quite a bit (16.4%) or definitely (8.2%) likely that someday they would have a prophylactic oophorectomy.

As expected, perceived risk of developing ovarian cancer was positively correlated with intention to undergo prophylactic oophorectomy, $r = 0.51$, $p < .01$. Further, consistent with findings from previous studies, high monitoring (as determined by a median split) was associated with higher perceived risk for developing ovarian cancer someday (rated on a 0-100% scale), $r = 0.35$; $p<.05$, and with greater intention to undergo prophylactic oophorectomy, $r = 0.42$, $p < .05$.

To date, we have analyzed data from 64 women who have completed the 3-month assessments. To examine women's changes in intention to undergo surgery, we computed a change score by assessing the difference in women's intentions from baseline to 3-months post-baseline (i.e., a positive score represents a shift toward greater intention to have surgery). Regression analyses indicated that a shift toward greater intention to undergo surgery was associated with the use of seeking emotional support as a coping strategy ($\beta = .43$, $t = 2.78$, $p < .01$) and younger age ($\beta = -.32$, $t = -1.91$, $p = .06$), but not associated with subjective or objective risk status, perceived barriers to surgery, or knowledge.

This research has resulted in the following conference presentations:

Fang, C.Y., Miller, S., Daly, M., Ohls, L., & Hurley, K. (1999). Monitoring attentional style and interest in prophylactic oophorectomy. Poster presented at the 23rd Annual Meeting of the American Society of Preventive Oncology, March 14-16, 1999, Houston, Texas.

Fang, C.Y., Miller, S.M., Daly, M.B., Ohls, L.M., and Hurley, K. (1999). Psychological factors associated with intention to undergo prophylactic oophorectomy. Poster presented at the 20th Annual Convention of the Society of Behavioral Medicine, March 3-6, 1999, San Diego, California.

Fang, C. Y., Miller, S. M., Longacre, M., Hurley, K., & Daly, M. B. (2001). Decision making about prophylactic oophorectomy. Poster presented at the 25th Annual Meeting of the American Society of Preventive Oncology, March 12-13, 2001, New York, New York.

Miller, S.M. Decision making and prophylactic oophorectomy. Part of Symposium on Decision Making and Genetics. Conference on Enhancing Outcomes in Women's Health: Translating Psychosocial and Behavioral Research into Primary Care, Community Interventions and Health Policy. Washington, D.C., February, 2002.

Fang, C.Y., Miller, S.M., Malick, J., & Daly, M.B. Coping predicts changes in intention to undergo prophylactic surgery. Submitted to the 23rd Annual Convention of the Society of Behavioral Medicine, April, 2002.

Finally, based on work supported by this award, we have applied for funding from the Cancer Research Foundation of America for our proposal entitled, "A Systematic Evaluation of the Short- and Longer-Term Psychosocial Impact of Ovarian Cancer Early Detection Surveillance" (P.I.: Suzanne M. Miller, Ph.D., submitted September 15, 2001).

CONCLUSION

This research will fill a void in the ovarian cancer risk literature. Women with an increased risk of ovarian cancer face a difficult decision regarding preventative surgery, and few resources are available to help them with their decision. Hence, it is important to explore factors associated with decision-making and to use the information to develop effective counseling interventions. Through more systematic investigation of these factors, we will be able to develop a profile of

decision making that will be used to design an enhanced counseling intervention. A pilot study will then investigate the effectiveness of the resulting counseling intervention.

REFERENCES

Miller, S. M., Fang, C. Y., Manne, S. L., Engstrom, P. F., & Daly, M. B. (1999). Decision making about prophylactic oophorectomy among at-risk women: Psychological influences and implications. *Gynecologic Oncology, 75*, 406-412,

Hurley, K.E., Miller, S.M., Costalas, J.W., & Daly, M.B. (2001). Anxiety/uncertainty reduction as a motivation for interest in prophylactic oophorectomy in women with a family history of ovarian cancer. *Journal of Women's Health and Gender-Based Medicine, 10*, 189-199.

Fang, C. Y., Miller, S. M., Daly, M. B., & Hurley, K. (in press). The influence of coping style and risk perceptions on decisions to undergo prophylactic oophorectomy among FDRs. *Psychology & Health.*.

ANNUAL REPORT – YEAR THREE

PROJECT III

PHASE II CHEMOPREVENTION STUDY OF OVARIAN CANCER

Project Director **Robert F. Ozols, M.D., PH.D.** **Fox Chase Cancer Center**

INTRODUCTION

Fenretinide, a retinamide derivative of vitamin A, is a promising chemopreventive agent, which induces apoptosis and decreases cell proliferation. It has an inhibitory effect on the growth of ovarian cancer cells and surface epithelial cells of the ovary. This research study tests the hypothesis that treatment of high-risk individuals with fenretinide will change the histologic features associated with a preneoplastic phenotype in ovaries as well as alter putative biomarkers of preneoplasia. To test our hypothesis we are conducting a Phase II clinical trial of fenretinide versus a placebo in women with high risk of developing ovarian cancer and a desire to undergo oophorectomy for prophylaxis. At the completion of the treatment phase of the clinical trial, all patients will undergo oophorectomy, and the histologic characteristics of the ovaries from the two groups of patients will be compared as well as markers of cell proliferation and apoptosis. In addition, these results will be compared to ovaries removed from untreated individuals at no increased risk for ovarian cancer. This study will establish baseline values of SEBs in high-risk and normal-risk populations as well as evaluate the specific effect of fenretinide treatment on cell proliferation and apoptosis in precursor lesions of an ovarian cancer-prone population.

BODY

A total of 71 participants (including a 10% "drop-out" rate) will be randomized to allow 32 evaluable participants per arm. Eligible to participate are women greater than 18 years of age who have decided to undergo a prophylactic oophorectomy due to increased risk for ovarian cancer defined by: 1) evidence of a genetic defect in BRCA1 or BRCA2, or 2) one or more first-degree relatives diagnosed with ovarian cancer prior to the age of 50 years, or 3) other family history contributing to risk: one first-degree relative diagnosed with ovarian cancer at any age and at least one other first- or second-degree relative diagnosed with ovarian cancer at any age.

Participants are randomized to take daily oral doses of either 400 mg 4-HPR or placebo for 4-6 months with monthly 3-day drug holidays. Following this treatment period, the participant undergoes the planned prophylactic oophorectomy 7-10 days after the first day of her menstrual cycle. The primary objectives are to assess the effect of 4-HPR on ovarian histology; and the effect of 4-HPR on potential surrogate endpoint biomarkers (SEBs): apoptosis (TUNEL and immunohistochemistry of single-stranded DNA), apoptosis (regulation (bcl-2 and Bax expression), and one marker of proliferation (MIB-1 protein level). Additional control ovarian tissue will be obtained from: 1) high-risk individuals who are eligible for the trial but uncomfortable waiting 4-6 months for their oophorectomy, and 2) normal, low-risk individuals. These banked tissue samples will assist in evaluating the variability between individuals over time and the significance of SEBs for ovarian cancer. The total duration of the study is three years.

In May 1998, the Department of Defense notified the FCCC of its recommendation to fund our clinical prevention trial "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer." The study was submitted to the FCCC Research Review Committee (RRC) in June 1998. This committee reviews proposed clinical studies from the perspective of scientific rationale, study design, feasibility and conduct, patient registration and data management, statistical appropriateness and institutional priority. Additional information and revisions were

requested by the RRC. Following institution of these changes, the study was approved by the RRC and submitted to the Institutional Review Board (IRB).

In August 1998, this IRB-approved clinical trial was reviewed by the Surgeon General's Human Subjects Research Review Board (HSRRB). Additional clarifications were requested and instituted. Approval was granted.

In February 1999, this study underwent review by the National Cancer Institute, Chemoprevention Branch (NCI, CB). The NCI, CB is very supportive of this study and is providing fenretinide as well as placebo. The NCI has certain responsibilities as Sponsor for the Investigational New Drug application (IND) of fenretinide. In order for the NCI, CB to fulfill its responsibilities, the protocol, associated case report forms, and consent were revised for submission to the Federal Drug Administration (FDA) as part of the fenretinide IND application.

In June 1999, this study underwent review and approval by the FDA as part of the fenretinide IND application. In late June 1999, FCCC received fenretinide and placebo from the NCI.

The research protocol review and approval process was complicated and lengthy. As summarized in Table 1, 31 women have been recruited to the study. To date, 4 women have been evaluable per the protocol. Three individuals were enrolled to the ovarian tissue donation portion of the study and have already donated ovarian tissue at the time of their surgery. One woman was randomized to fenretinide or placebo for four months prior to her prophylactic oophorectomy, which was performed in March of 2000.

Recruitment through the family risk assessment program at FCCC continues. Genetic counselors at academic institutions in Pennsylvania have been contacted and given study information to provide to eligible women they may be counseling.

The Gynecologic Oncology Group has implemented this important study through their cooperative group mechanism. This will not only assist in accrual of this limited population but will make this scientifically interesting study available to high-risk women around the country.

KEY ANTICIPATED RESEARCH ACCOMPLISHMENTS

Anticipated key research accomplishments emanating from this research include the following:

- Success in altering the SEBs in this clinical trial format would justify prolonged treatment with fenretinide and provide an alternative to oophorectomy for prophylaxis in women at high risk for ovarian cancer.

- Tissues obtained during this research will be a resource for further studies of molecular carcinogenesis in ovarian cancer. This effort may lead to the identification of specific novel targets for therapy and prevention in patients with hereditary ovarian cancer and the more common sporadic epithelial ovarian cancer.

REPORTABLE OUTCOMES

The research protocol review and approval process was complicated and lengthy. Thus, no individuals have been enrolled to date. However, during this process, data collection and management systems were created in preparation for study activation.

1. Data Entry, Management and Quality Control

The large volume of information to be generated in this project requires the implementation of computer-based tools for the management and coordination of data. The Population Informatics Facility (PIF) is responsible for all database and statistical programming aspects of this study. The purpose of the PIF is to provide Informatics expertise to facilitate the research conducted by investigators at FCCC. PIF personnel designed and developed the appropriate database, created the data entry interface, trained the technicians in its use, and provided regular feedback on data quality.

At recruitment, each subject will be given a unique identification number. Baseline information on health, family and dietary history, along with pretreatment laboratory and clinical test results will be entered onto prepared hardcopy (paper) data collection instruments by a study representative. Upon completion, these forms will be sent to the FCCC Chemoprevention Protocol Office (CPO) where the data will be entered via terminals into the database using the electronic data system created by PIF programmers.

At each subsequent follow-up contact, a study representative will complete hardcopy questionnaires containing information on study subject compliance with pill consumption, toxicity symptoms, results of routine blood sample analyses, and clinical observations made by the attending physician. Similarly, the study representative will place results from all laboratory procedures on hardcopy data collection instruments. These forms will be sent to the Protocol Coordinator for data entry. All laboratory records will include the unique identifier and date of collection of the biologic sample.

The information system for this project was built on the system that has been developed by PIF to support the Chemoprevention Clinical Trials at FCCC. As of May 1, 1999, the Chemoprevention Clinical Trials database stores information on 1,526 study subjects from seven chemoprevention trials at FCCC. This DBMS maintains all of the data collected in these studies and is designed to facilitate many aspects of data collection and patient tracking. Based upon the data entered into the database, this software system is capable of performing such tasks as the determination of study eligibility, automated subject randomization and the generation of mailed reminder letters. Most, if not all, of these capabilities have been incorporated into the systems developed for this project.

The existing database management system uses the relational database product ORACLE as the primary software platform for data entry and validation, storage, retrieval, modification, and security. This software system runs on a UNIX-based distributed computing system. These computers are maintained by the Research Computer Services facility at the Fox Chase Cancer Center. This distributed computing system is an integral part of a Local Area Network (LAN) which provides connections to a Digital VAX computer, IBM compatible PC's, Macintoshes,

printers, plotters, and the Internet. The software developed to meet the needs of this study will also use these computing facilities.

On-screen data entry forms, designed to resemble the data collection instruments, were created using the ORACLE Forms V6.0 software. Data validation will occur both during and after data entry. Range, validity and logical consistency checks will be conducted during the data entry process to ensure data quality. Reports generated from the entered data will be compared to the original data collection instruments to further ensure the accuracy of the data stored on magnetic media. Edits will be conducted using the query-by-form capability of ORACLE. This system of data entry and corrections will allow the data analyst to have access to the most up-to-date and accurate data at any given time. Daily backups of the database will be conducted to protect against accidental corruption or deletion of the data. Statistical computing will be performed using a variety of statistical packages including SAS, BMDP, IMSL, Splus and other custom written programs.

In order to preserve privacy and confidentiality, a series of security measures will be undertaken. Only the person-specific identifier, and date of collection when appropriate, will be stored with study results. Lists of Ids matched with names and addresses will be stored by the investigators in locked filing cabinets. Further, through the use of the security measures available within the operating system (UNIX) and the relational database management software (ORACLE), restrictions will be applied to each user commensurate with their needs to access the data. All new personnel with any access to the data will be trained in the ethics of electronic data access.

2. Case Reports Forms

Data from these studies will be kept in a database consisting of 14 data "tables": (1) Initial Contact/On-study; (2) Eligibility Checklist; (3) Health History Data; (4) Baseline Epidemiologic Data (e.g., smoking and alcohol intake, reproductive history, weight, etc.); (5) Concomitant Medications; (6) Diet Data; (7) Pretreatment signs and Symptoms; (8) Physical Examination; (9) Study Drug Administration; (10) Compliance Measures; (11) Toxicities; (12) Routine Laboratory Studies (e.g., CBC, electrolytes, liver function tests, etc.); (13) Research studies (Mib-1, apoptosis markers, etc.); and (14) Off-study. Some of these tables will have one record per subjects (e.g., Health History Data) while other may have multiple records per subject (e.g., Toxicities), each identified by the individual-specific identification number and date of collection. All tables can be linked by their unique individual identification number (and date of collection, when appropriate).

3. Ovarian Tissue Analysis (Andres Klein-Szanto, M.D., Ph.D.)

Previous research done in our Institution using ovarian tissues from individuals with an inherited predisposition for ovarian cancer indicated that preinvasive lesions probably precede the development of ovarian cancer (1). The histological features of the ovaries from a number of such individuals were compared to ovaries from individuals at no increased risk for ovarian cancer. This study revealed two important findings. First, examination of the ovaries from twenty high-risk individuals revealed two unanticipated near-microscopic malignant common epithelial tumors. The second finding in this early study relates to the histological features of the ovaries in which cancer is likely to develop. These structural features or ovarian surface epithelium (OSE)

lesions are: surface papillae, invaginations, inclusion cysts, pseudostratfication or hyperplasia and stromal activity or nodularity. The cancer-prone ovaries contained a range of histological features not usually seen in such magnitude, combination and complexity in control ovaries. A significant number of cases (70% of high-risk ovaries versus 20% of the control group of ovaries) presented multifocal surface papillomatosis ranging from a few foci to markedly extensive. These projections were usually short and stubby, with a fibrous core covered by cuboidal or pseudostratified epithelium. The invaginations were often very deep into the cortex, sometimes with bifurcations or branching. Similar but fewer and less deep invaginations were also observed in 11 of 20 control ovaries.

Another frequent finding in the cancer-prone ovaries was the presence of cortical superficial "inclusion" cysts in 70% of high-risk cases versus 25% of controls. They were of variable size and shape, usually lined by a pseudostratified epithelium of "serous" or tubal type and usually devoid of any contents within the space. In some cases, groups of the cysts of varying complexity occured creating the appearance of microscopic cystadenomas or adenofibromas.

Occasional mitoses and apoptotic cells were observed in the surface epithelium of cancer-prone ovaries associated with an increase in height and pseudostratification of the tall columnar cells.

In addition to the OSE lesions, the stroma of these organs also appeared to be uncharacteristically active or hyperplastic.
Several later publications published in the last two years have revisited this topic and have reached similar conclusions (2-5). Werness et al (2) found that cancer prone ovaries had significantly more cysts, cortical nodularity and OSE cellular atypia than control ovaries. Casey et al (3) found more surface papillae in ovaries from BRCA1 and BRCA2 patients and Sherman et al (4) and Deligdisch et al (5) concluded that epithelial hyperplasia and atypia are more frequent in susceptible populations than in control patients. Conversely a couple of publications found no significant differences in lesion incidence between ovaries from cancer prone patients and control ovaries (6-7).

During the course of this project we have analyzed a new set of tissues derived from patients with either BRCA1 or BRCA2 mutations (n=29). We compared the OSE lesions in these tissues with those from a control age-matched population (n=27) that underwent oophorectomy for unrelated disease (leiomyomata, cervical cancer and intestinal disease). The cancer prone patients were from the surgery-only arm of our study and did not receive any chemopreventive treatment. The controls were from our archival surgical pathology collection. The tissues were examined separately by two pathologists in a blind fashion. Both invaginations and inclusion cysts were seen more frequently in the high risk population than in the control tissues ($p<0.001$). The incidence of the other OSE lesions were not found to be statistically different in these two groups.

We investigated the proliferative characteristics of the surface epithelium of these samples Using the proliferative marker Mib-1 we found that the Mib-1 index (percent of positively stained cells or labeling index, LI) of the apparently normal surface epithelium was very low and not significantly different in the two groups. (LI range 0 to 1). Although some differences in LI were found in cysts, invaginations, and papillae , these were not statistically significant. In a few cases

the from cancer prone subjects papillae and cysts had a LI as high as 9%, nevertheless no statistically differences were noted when compared with the control cases.
In conclusion, our new study did not find significant proliferative changes in lesions from ovaries derived from patients at high risk but confirmed previously published results from our own Institution and others indicating that some of these OSE lesions are seen more frequently in ovaries from cancer-prone individuals.

4. Publications/Presentations

1. Salazar H, Godwin A, Daly M, Laub P, Hogan W, Rosenblum N, Boente M, Lynch H, and Hamilton T. Microscopic benign and invasive malignant neoplasms and a preneoplastic phenotype in prophylactic oophorectomies. J Natl Cancer Inst 88:1810-1820, 1996.

2. Werness BA, Afify AM, Bielat KL, Eltabbakh GH, Piver MS, Paterson JM. Altered surface and cyst epithelium of ovaries removed prophylactically from women with a family history of ovarian cancer. Hum Pathol 1999;30(2):151-7.

3. Casey MJ, Bewtra C, Hoehne LL, Tatpati AD, Lynch HT, Watson P. Histology of prophylactically removed ovaries from BRCA1 and BRCA2 mutation carriers compared with noncarriers in hereditary breast ovarian cancer syndrome kindreds Gynecol Oncol 2000;78:278-87.

4. Deligdisch L, Gil J, Kerner H, Wu HS, Beck D, Gershoni-Baruch R. Ovarian dysplasia in prophylactic oophorectomy specimens: cytogenetic and morphometric correlations.Cancer 1999;86:1544-50.

5. Sherman ME, Lee JS, Burks RT, Struewing JP, Kurman RJ, Hartge P. Histopathologic features of ovaries at increased risk for carcinoma. A case-control analysis. Int J Gynecol Pathol 1999 ;18:151-7.

6. Barakat RR, Federici MG, Saigo PE, Robson ME, Offit K, Boyd J Absence of premalignant histologic, molecular, or cell biologic alterations in prophylactic oophorectomy specimens from BRCA1 heterozygotes.Cancer 2000;89:383-90.

7. Stratton JF, Buckley CH, Lowe D, Ponder BA. Comparison of prophylactic oophorectomy specimens from carriers and noncarriers of a BRCA1 or BRCA2 gene mutation. United Kingdom Coordinating Committee on Cancer Research (UKCCCR) Familial Ovarian Cancer Study Group. J Natl Cancer Inst 1999 ;91:626-8.

Paul F. Engstrom, M.D. presented an overview of this study at the European School of Oncology meeting, September 12-14, 2001, Moscow, Russian Federation.

CONCLUSIONS

The accrual to this study has been unacceptably slow. Two women consented in 1999, five in 2000. There was no accrual in 2001. Of the 7 participants accrued, 6 were tissue

donation only; one woman took the drug (fenretinide or placebo). There were no reportable SAEs for the trial. No one is currently enrolled in the study.

In October 2001, the Cooperative Group version of the protocol GOG-0190 will be reviewed by the Fox Chase Cancer Center Institutional Review Board. In the new study design, there is no "tissue only" option; women will consent to be randomized to either immediate prophylactic oophorectomy or to drug for four months followed by prophylactic oophorectomy. We plan to support the tissue analysis portion of the trial on the Ovarian SPORE grant; the Gynecological Oncology Group will be responsible for monitoring accrual, interim reports and analysis of the results of this protocol.

A Phase II Evaluation of Fenretinide (4-HPR) as a Chemopreventive Agent for Ovarian Carcinoma
RECRUITMENT

Study #	Screening Date	Referral	Eligible Yes/No	Enrolled Yes/No	Reason Not Enrolled	Date Of Consent	Arm: D=drug vs. T=tissue only
6001	08/16/99	FRAP	Y	Y	-	10/29/99	D
6002	07/20/99	FRAP	Y	Y	-	11/18/99	T*
6003	08/02/99	FRAP	Y	Y	-	02/09/00	T**
6004	08/02/99	FRAP	Y	N	Undecided- seeking 2nd opinion	-	-
6005	08/02/99	FRAP	Y	N	Undecided	-	-
6006	08/02/99	FRAP	Y	N	Undecided	-	-
6007	08/02/99	Boente	Y	N	Had 2nd ovary removed in 3/99	-	-
6008	08/08/99	FRAP	?	N	No response from participant	-	-
6009	08/09/99	FRAP	Y	N	Emergency oophorectomy -9/99	-	-
6010	08/22/99	Internet	Y	N	undecided	-	-
6011	10/26/99	FRAP	N	N	Surgery not recommended by MD	-	-
6012	11/18/99	Internet	N	N	Currently being treated for breast ca	-	-
6013	01/03/00	Friend/FOCUS	N	N	Surgery scheduled- 01/10/00	-	-
6014	01/04/00	FOCUS	N	N	Has not spoken to MD/Gyn nor undergone counseling	-	-
6015	01/04/00	FOCUS	N	N	Currently being treated for breast ca and has not received genetic counseling.	-	-
6016	01/06/00	Unknown	N	N	Gyn doesn't agree with surgery nor has patient undergone counseling.	-	-
6017	01/31/00	Boente	N	N	Has not undergone genetic counseling	-	-
6018	01/10/00	FOCUS	N	N	Has not undergone genetic counseling	-	-
6019	03/01/00	Internet	N	N	Did not meet criteria- cystic disease	-	-

*could not d/c NSAID

** taking oral contraceptives for ovarian cysts

Study #	Screening Date	Referral	Eligible Yes/No	Enrolled Yes/No	Reason Not Enrolled	Date Of Consent	Arm: D=drug vs. T=tissue only
6020	03/03/00	FRAP	Y	Y	Currently taking Prempro. Colonscopy scheduled 3/22/00 for + quaiac. Will call when ready for surgery.	-	-
6021	03/03/00	FRAP	Y	Y	Undecided bewteen ooph or hyster. OV with Daly on 4/28 to make final decision. Possibly tissue only.	-	-
6022	03/29/00	FRAP	Y	N	Undecided		
6023	05/10/00	FRAP	Y	Y	-	05/23/00	T
6024	03/23/00	FCCC-Website	N	N	Has not undergone genetic counseling	-	-
6025	05/05/00	Bergman clinic	Y	Y	Undecided- may postpone surgery for years	-	-
6026	05/19/00	Bergman clinic	Y	Y	Undecided	-	-
6027	05/04/00	Bergman clinic	N	-	Has not undergone genetic counseling	-	-
6028	06/28/00	FRAP	?	N	Diagnosed with (?) ovarian cancer prior to decision with M.D. for surgery	-	-
6029	05/30/00	Email through Ozols	?	?	May postpone surgery until menopause	-	-
6030	07/19/00	Bergman clinic	?	N	Has not undergone genetic counseling	-	-
6031	07/20/00	FRAP	Y	N	Undecided- may do surgery sometime during the winter	-	-
6032	09/25/00	FRAP (Network)	Y	N	Doesn't want surgery for another 1-2 years	-	-
6033	12/11/00	Relative who underwent genetic counseling	N	N	Early on decision making process (info seeking) lives in North Carolina	-	-

Study #	Screening Date	Referral	Eligible Yes/No	Enrolled Yes/No	Reason Not Enrolled	Date Of Consent	Arm: D=drug vs. T=tissue only
6034	12/18/00	FRAP	Y	N	Not sure yet if/when surgery	-	-

ANNUAL REPORT – YEAR THREE

LABORATORY CORE

Core Director **Andrew K. Godwin, Ph.D.** **Fox Chase Cancer Center**

INTRODUCTION:

The molecular genetic events involved in the development of ovarian cancer are poorly understood. Ovarian cancer is the number one gynecologic killer in the United States with over 25,000 diagnosed cases and 14,500 deaths in 1999. A major reason for the high morbidity and mortality associated with ovarian cancer relates to the patterns of dissemination and the absence of signs or symptoms associated with early stage disease. Consequently, most patients are diagnosed with advanced stage (International Federation of Gynecology and Obstetrics [FIGO] III-IV) disease; five-year survival rates for this group of patients are only 20-30%. In contrast, five-year survival rates for patients with limited-stage disease (FIGO I-II) are 70-90%. Thus, understanding the etiology of ovarian cancer remains an important challenge in molecular genetic research. Ultimately, this knowledge may enable the development of better approaches for earlier diagnosis, allowing current therapeutic strategies to be more effective. To support these kinds of studies large numbers of biosamples from well-staged and managed cancer patients and controls is needed. Therefore, the laboratory core was created to collect normal and tumor ovarian tissue as well as blood samples that can be made available for a variety of researcher projects.

BACKGROUND:

The Laboratory Core of the Ovarian Cancer Prevention Program of Fox Chase Cancer Center funded by the Department of Defense, is responsible for the collection, storage, and distribution of biosamples collected as a result of the "Ovarian Cancer Consortium for Research and Surveillance (OCCRS)" and the "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".

BODY:

The goals of this laboratory core have been met (i.e., collect and distribute biosamples), however the number of participants recruited into the Ovarian Cancer Consortium for Research and Surveillance (OCCRS) and the fenretinide chemoprevention study were less than predicted. Nevertheless, the number of blood samples obtained from OCCRS participants increased steadily over the course of the grant.

SPECIFIC AIMS (PREVIOUSLY PROPOSED):

***Specific Aim 1: Collection and banking of blood samples from women with ovarian cancer, and their first- and second-degree relatives as part of the* "Ovarian Cancer Consortium for Research and Prevention".**

Results:

Six hundred and eighty-seven (687) participants, including 234 ovarian cancer patients and representing 320 families are enrolled. Two hundred thirty-one (231) families had one case of ovarian cancer, 52 had two cases and 21 had more than two. One hundred seventy-four (174) families had both breast and ovarian cancer, supporting the clustering of these cancers in women with BRCA1 and BRCA2 mutations. The median age of OCCRS participants is 48 years, with a

range of 16 to 93 years. The geographic base of recruitment has increased significantly due to networking with national advocacy organizations such that women in 42 states and Canada are enrolled. In support of the OCCRS (**Project 1; "Ovarian Cancer Consortium for Research and Surveillance**"), the Core laboratory has collected, processed and banked biospecimens (e.g., serum, platelets, DNA, and lymphocytes) from 469 blood samples.

1) 469 blood samples have been collected through the Ovarian Cancer Consortium for Research and Surveillance.

2) 469 blood samples have been process and the serum, platelets, and lymphocytes were banked and genomic DNA isolated from "buffy coats".

3) 545 samples (either DNA or whole blood) recruited through the Ovarian Cancer Clinical Network were distributed to program project participants and FCCC Investigators (275 whole blood samples to Dr. R. Raftogianis, FCCC, 150 DNA's to A. Yeung, FCCC, and 120 DNA's to T. Hamilton, FCCC).

Change in personnel/facilities:

To improve and standardize the collection and processing of blood samples, FCCC established under the direction of Dr. Godwin, the Biosample Repository in November of 1999. This new laboratory is located on the second floor of the Cancer Prevention Pavilion and occupies ~900 square feet of space with the appropriate equipment including liquid nitrogen freezer space to bank ~72,000 cryovials.

Ms. J. Dangel, Chief Technician in the Department of Pathology at the Fox Chase Cancer Center, was appointed manager of the Biosample Repository in 1999 and was responsible for CAP accreditation and CLIA approval. Her roll is to process blood samples submitted to the Repository (through the Ovarian Cancer Consortium for Research and Surveillance). Samples to be tested for mutations in *BRCA1* and/or *BRCA2* are submitted to Clinical Molecular Genetic Laboratory at FCCC. Ms. Dangel is also responsible for entering collection data regarding the biospecimens into the centralized computer database.

Specific Aim 2: ***Collection and distribution of archival ovarian tumor and prophylactic oophorectomy specimens as part of the*** **"Ovarian Cancer Consortium for Research and Prevention".**

Results:

1) 34 ovarian tumor specimens were collected following surgery at Fox Chase/American Oncologic Hospital and were flash-frozen and stored in liquid nitrogen.

2) 96 fresh-frozen ovarian tumors were given to Dr. J. Testa (FCCC) to evaluate the levels of activity of AKT, AKT2, and AKT3.

3) 22 DNA's from ovarian tumor showing LOH on 6q (and matching constitutive DNA-see above) were given to Dr. T. Hamilton to support mutational analysis of *LOT-1*.

4) During the course of the grant we collected ovarian tissue from 37 women, ages ranging from 34 to 79 years of age. The samples have been collected from 27 different hospitals throughout the United States. Tissue collected at sites other than Fox Chase are arranged through the attending pathologist at the off campus site and a kit is mailed to either the surgeon or the pathologist.

a) Eight (8) of the women were determined to have a *BRCA1* mutation.

b) Three (3) of the women were determined to have a *BRCA2* mutation.

c) Three (3) of the women are from families with a mutation in *BRCA1* (2) or *BRCA2* (1). However, the individuals have declined clinical genetic testing. We are currently screening DNA samples isolated from ovarian tissues to determine if the women from these *BRCA1* or *BRCA2* mutation families are carriers.

d) Thirteen (13) are from families with a history of breast/ovarian cancer which have not yet been tested for *BRCA1* or *BRCA2* mutations

e) Ten (10) are from families with no family history of breast or ovarian cancer, which have tested negative for a *BRCA1* or a *BRCA2* mutation.

f) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

5) Primary cell lines were generated from the ovaries of the *BRCA1* and *BRCA2* mutation carriers as well as control individuals.

a. These cell cultures are being used in a collaborative study with Dr. A. Knudson (Senior Member, FCCC) entitled "Evaluation of *in vivo* and *in vitro* pharmacology and toxicology of preventative agents using human mutant cells from dominantly heritable cancers" to study the changes in gene expression following treatment with a variety of chemoprevention agents in culture.

b. Three (3) primary human ovarian surface epithelial (HOSE) cell cultures and 3 mortal, SV40 expression and 3 matching immortal SV40 expressing HOSE cell lines were given to Drs. P. Engstrom (P.I.) and C. Patriotis (Associate Member, FCCC) for evaluation of changes in gene expression patterns following 4-HPR treatment.

***Specific Aim 3: Collection and processing of prophylactic oophorectomies from women participating in the chemoprevention trial as part of the* "Evaluation of Fenretinide as a Chemopreventive Agent for Ovarian Cancer".**

Results:

In order to find women eligible for the 4-HPR trial, we have tested a number of participants of the FRAP for mutations in *BRCA1* and/or *BRCA2* as outlined below. Genetic testing is not funded through this application, but is necessary to increase the pool of women likely to elect to undergo prophylactic surgery.

1) DNA samples from a total of 480 individuals (obtained through the OCCRS or high-risk clinics at FCCC) were tested (either partially or completely) for mutations in *BRCA1* and/or *BRCA2* during the last year

a) 480 DNA samples were tested for three Ashkenazi Jewish founder mutations (i.e., 185delAG and 5382insC for *BRCA1*, and 6174delT for *BRCA2*) using a Heteroduplex Mobility Assay (HMA).

b) 158 samples were tested for mutation in 23 exons and a limited number of adjacent intronic base pairs of *BRCA1* using an enzymatic mutation detection (EMD) assay and direct sequencing.

c) 45 samples were tested for mutations in 26 exons and a limited number of adjacent intronic base pairs of *BRCA2* by direct sequencing.

2) Genetic test results were given to Dr. M. Daly (Senior Member, Director of the Family Risk Assessment Program) and *BRCA1* and *BRCA2* mutation carriers were approached for participation in the 4-HPR chemoprevention trial.

3) Ovarian tissue specimens were collected from 2 women who elected to undergo prophylactic oophorectomies at Fox Chase

a) The two women that participated on the 4-HPR trial reported a family positive family history of breast and ovarian cancer, but had not been previously tested for a *BRCA1* or a *BRCA2* mutation.

b) Tissue sections of all of the ovaries were given to Dr. A. Klein-Szanto for immunohistochemical staining of various markers and pathological review.

c) DNA was isolated from the ovarian tissue and is being evaluated in the Clinical Molecular Genetics Laboratory for mutations in either *BRCA1* or *BRCA2*.

4) A limited number of DOD participants have been tested for germline mutations in *BRCA1* and/or *BRCA2*. Four (4) *BRCA1* have been detected in 33 of the participants which were randomly selected and twenty-three (23) mutations in *BRCA1* and/or *BRCA2* were uncovered in women of Ashkenazi Jewish heritage. Further studies by our group are scheduled to determine the prevalence of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada (as indicated below).

KEY RESEARCH ACCOMPLISHMENTS:

- Obtained and banked 469 blood samples into the OCCRS during the course of the grant.
- Distributed DNA from blood and ovarian tumors to multiple investigators for various studies (as outlined below).
- Collected 37 overtly normal ovaries from women undergoing oophorectomies. Two of these individuals had participated on the 4-HPR chemoprevention trial.
- Identified 36 germline mutations in the OCCRS participants.

REPORTABLE OUTCOMES:

- In total we have collected 64 ovaries (27 women donated both their left and right ovaries, 6 donated only the left ovary, and 4 donated only the right ovary). We have successfully initiated primary HOSE cell cultures from many of these tissues.

CONCLUSIONS:

Collection of ovarian cancer tissue (tumor and normal) and blood biospecimens is ongoing, due in part to the high compliance rate of the participants. Laboratory research is underway using DNA from these samples to:

1) Determine the prevalence of germline *BRCA1* and *BRCA2* mutations in population-based samples of ovarian cancer cases in the U.S. and Canada.

2) Estimate the penetrance of germline *BRCA1* and *BRCA2* mutations and compare these estimates across:

a) genes (*BRCA1* vs. *BRCA2*)

b) mutation type (Ashkenazi Jewish founder mutations vs. all others)

c) method of family ascertainment

3) Identify novel genetic polymorphisms in the human arylsulfatase gene from 150 samples; a SNP in the 3'-flanking region has been identified.

4) Identify common alleles in the human UDP-glucuronosyltransferase gene, *UGT1A6*. Thus far four common alleles have been identifies and will be further characterized for functional significance with funding from a DOD Breast Award.

5) Identify novel genetic polymorphisms in the human sulfotransferase gene, *SULT2B1*; this project is in the beginning stages.

6) Determine if *LOT*-1 on chromosome 6q is maternally imprinted and if loss of the paternal allele is involved in ovarian carcinogenesis.

7) Determine if germline mutations (and/or polymorphisms) in various repair genes are present at a higher frequency in 100 ovarian cancer patients as compared to 100 age-matched controls.

Overall, we have established a valuable resources through the Core laboratory that will continue to provide important insights with regard to molecular genetic mechanisms associated with ovarian epithelial oncogenesis as well as a better understanding of the biological and biochemical pathways which are altered in response to chemopreventive treatments. The samples will continue to be made available through the Biosample Repository at FCCC and through support of the NIH.

ANNUAL REPORT – YEAR THREE

DATA MANAGEMENT CORE

Core Director **Eric A. Ross, Ph.D.** **Fox Chase Cancer Center**

INTRODUCTION:

The varied populations studied in this Ovarian Cancer Prevention Program and the complexity of the designs requires the development and support of program-specific computer based tools to provide critical project management and coordination, and for the collection, validation, storage, retrieval and analysis of data. The projects contained in this program project grant (PPG) include: the Ovarian Cancer Consortium for Research and Surveillance, the Facilitating Decision-Making About Prophylactic Oophorectomy, and the Phase II Chemoprevention Study of Ovarian Cancer studies.

The specific aims of the Data Management Core (Core) are:

1. Provide computer-based tools that facilitate the entry, storage, manipulation and retrieval of the large quantities of data generated.
2. Ensure the accuracy of the data maintained in the database by developing human and software based data consistency and quality control systems.
3. Provide high-quality data entry services.
4. Organize and maintain the database to maximize accessibility, while maintaining strict confidentiality.
5. Provide statistical computing support.

BODY:

Statement of Work:

Months 1-12: (1) Core staff will meet with research staff to refine and finalize the data flow and hardcopy data collection instruments. (2) Data Dictionaries will be developed. (3) Database design will be finalized by the Facility Director and Database Programmers. (4) The database management systems developed for the FRAP/CFRBCS project and the Chemoprevention Clinical trials will be modified to implement the database for this program project. (5) Electronic data entry forms will be designed, and implemented by the Database Programmers. (6) Software for the scheduling of follow-up visits, the distribution of mailed self-report questionnaires, and the generation of contact logs for conducting telephone interviews will be developed. (7) All software will undergo thorough testing.

Months 3-36: (1) Data quality assurance and quality control procedures will be developed and implemented. (2) Research staff will be instructed in data coding procedures. (3) The Data Entry Clerk and laboratory technicians will be trained in the use of the electronic data entry forms. All data delivered to the Core will be efficiently and accurately entered by the Data Entry Clerk into the database. (4) Post-data entry, data validation software will be developed, tested and utilized. All data will be reviewed upon receipt and aberrant values will be corrected. (5) Daily backups of the database will be conducted.

Months 6-36: (1) The Database Programmer will perform all tasks necessary to ensure that the database functions in an efficient manner. The database will be modified by the Database Programmer, as necessary, to ensure that the database software meets the needs of the projects that compose the Program Project. (2) Software for the generation of reports concerning each

study's progress will be developed, tested and periodically executed. (3) Software to allow for the extraction of data for analysis purposes will be developed, tested and utilized upon request. (4) Statistical programming tasks may be conducted by Core staff under the direction of the study statisticians.

The goals of this core have been met.

KEY RESEARCH ACCOMPLISHMENTS:

- Core staff collaborated with project investigators and research staff to refine and finalize the data flow and hardcopy data collection instruments. Core staff developed data dictionaries based on the study requirements and the final data collection instruments.
- Core personnel have designed and developed a comprehensive information management system to meet the specific needs of this PPG. The customized relational database system has been implemented using ORACLE version 8 database software. The database and management structure allows efficient data capture and manipulation, as well as the controlled exchange of information across the several projects. All software underwent thorough testing before release to the user community.
- Client-server electronic data entry/retrieval and report generation software have been developed using the Oracle Developer/2000 suite of products.
- Data quality assurance procedures have been implemented, using software-based data entry checks as well as post-entry manual audits.
- Data entry services were being provided by a Core data entry clerk using the electronic data entry screens developed by Core programmers. Any observed aberrant data values were corrected in the database.
- Software for the scheduling of follow-up visits, and the distribution of mailed self-report questionnaires were developed and deployed.
- Software has been developed to generate reports to allow tracking of study accrual and progress of individual study subjects.
- Software has been developed for extracting data from the relational database.
- Core personnel supported all aspects of the information management system.
- The database was backed-up to tape on a daily basis. Periodically, a copy of the database backup tape was sent to an off-campus facility for secure storage. Username and password control were used to ensure that investigators and research staff only had access to the information approved for their use. All FCCC computers used for storing the information were protected from inappropriate outside access by the FCCC firewall.
- Core staff performed statistical programming using standard packages (e.g., SAS) under the direction of the study statisticians and investigators.

REPORTABLE OUTCOME:

All data collected in the three research projects as well as data generated by the Laboratory Core are being stored in this information system. The details of the information system developed for this the three research projects are described below.

Project I: The Ovarian Cancer Consortium for Research and Surveillance:

Included in this portion of the PPG information system is health history, clinical, epidemiologic, socio-demographic, psychosocial and laboratory data. In addition, this database contains cancer and vital status data on relatives of individuals recruited into the study. A web-enabled interface to the information system has been developed to maintain the biosample collection, preparation, shipping/receiving and inventory data. The software system coordinates numerous tasks, including the scheduling of follow-up visits, and the distribution of mailed self-report questionnaires. This system is capable of generating multigenerational pedigrees from the union of family histories provided by two or more distinct study subjects in the same family. The family data is easily updated from follow-up information to include deaths or new cancers reported for study subjects, previously listed family members, as well as new births. Currently, data from 687 live participants and 105 proxy questionnaires are stored in this database. The database also contains laboratory inventory and processing information on blood samples collected from 469 registry participants.

Project II: Facilitating Decision-Making About Prophylactic Oophorectomy:

The database system provides the means for entry, storage and manipulation of all the psychosocial, outcome and study-related data collected in this project. Software has been developed to automatically distribute mailed self-report questionnaires. Information obtained from 78 study subjects have been entered into the information system.

Project III: Phase II Chemoprevention Study of Ovarian Cancer:

The PPG relational database management system also maintains all of the information collected in this phase II clinical study including demographic, health history, pathology, laboratory, study status, adverse reaction and drug compliance data. The software system facilitates many aspects of data collection and patient tracking. This software system uses database information to perform such tasks as: determination of study eligibility, automated subject randomization, and automatic notification of the study biostatistician (via e-mail) of subject randomization. Since initiating the study, seven subjects have been identified as eligible for the protocol. One subject has been randomized.

CONCLUSIONS:

Ovarian cancer is the leading cause of death from a gynecologic malignancy among women in the United States, and ranks second in incidence among gynecologic malignancies. Fox Chase Cancer Center has conducted research in ovarian cancer prevention and control focusing on familial risk of cancer, the behavioral factors influencing the decision to undergo prophylactic oophorectomy, and the effect of chemoprevention agents on precancer structural and molecular markers of carcinogenesis.

This core served a resource for the PPG as a whole and maintains a valuable source of data for future studies. By centralizing these services into a Data Management Core, we were better able to manage and coordinate the collection, storage, and distribution of a large amount of highly valuable data. Subject to informed consent, the information contained in the data repository was available to all investigators in the PPG. By providing access to the data to all participants, sharing technical capabilities and ensuring the quality of the data, this core not only facilitated achievement of the aims of the individual projects, but also made possible exploratory analyses beyond the stated aims of the projects.

APPENDICES

A. Project I, Key Personnel

B. Project I, Focus on Ovarian Cancer Research Insert,
Prevention Matters Newsletter

APPENDIX A
KEY PERSONNEL

Fox Chase Cancer Center

Principal Investigator: Paul F. Engstrom, M.D.
Project Director: Mary B. Daly, M.D., Ph.D.
Co-Investigator: Andrew Godwin, Ph.D.
Co-Investigator: Betsy Bove, Ph.D.
Statistician: Andre Rogatko, Ph.D.
Project Manager: Carol Cherry, R.N.C., B.S.N., O.C.N.
Genetic Counselor: Josephine Costalas, M.S.
Administrative Assistant: Honey Salador
Data Management: Andrew Balshem
John Malick
Rose Batson
Director of Nursing Research: Andrea Barsevick, R.N., D.N.Sc.

Cooper Hospital/University Medical Center

Network Site Director: Generosa Grana, M.D.
Gynecology Oncology Group: David Warshal, M.D.
James Aikins, M.D.
Thomas Rocereto, M.D.
Genetic Research Coordinator: Evelyn Churchville Letarte, A.D.
Gynecologic Oncology Nurse: Wendy Topeka, R.N., B.S.N., O.C.N.

The Reading Hospital and Medical Center

Network Site Directors: Norman G. Rosenblum, M.D., Ph.D. & Terrance Cescon, M.D.
Cancer Center Program Manager: Patricia Weiser, R.N., C.C.R.A.
Family Risk Assessment Program Coordinator: Marilyn Brennan, R.N., O.C.N.

Wake Forest University Baptist Medical Center

Network Site Director: Electra D. Paskett, Ph.D.
Research Fellows: Lauren Bliss, M.D.
Kristie Long, Ph.D.

APPENDIX B

Focus on Ovarian Cancer Research Insert
Prevention Matters Newsletter

FOCUS ON OVARIAN CANCER RESEARCH

Quilt Exhibit and Reception Promotes Ovarian Cancer Awareness

The Family Risk Assessment Program hosted a quilt exhibit and reception at Fox Chase Cancer Center (FCCC) in support of ovarian cancer awareness. The quilts were displayed October 16-27, 2000 in the new Prevention Pavilion which allowed hundreds of patients, visitors and staff to view them. It was plain to see that the two quilts were truly labors of love. One was created by two close friends of Carolyn A. Marks, an ovarian cancer patient at FCCC who fought the disease until the fall of 1999. Carolyn organized the Philadelphia Chapter of the National Ovarian Cancer Coalition (NOCC), a group committed to raising awareness and promoting education about ovarian cancer. The quilt dedicated to Carolyn contained many of her personal items including jewelry, clothing and photos.

Originally conceived by ovarian cancer survivor and quilter, Shirlee Mohiuddin as a blanket of support for cancer patients, the quilts are now part of a public education initiative. Five different handmade survivors' quilts are available for display in local communities; arrangements can be made by contacting the Ovarian Cancer National Alliance (OCNA) at 202-331-1332.

The exhibit culminated in a reception on October 25, 2000 supported by Alza Pharmaceuticals and Bristol-Myers Squibb. Ovarian cancer survivors April Donahue, President of the Philadelphia Chapter of NOCC, and Marjorie Mac Nee, Coordinator of the Oncology Administrative Office at Crozer Regional Cancer Center, spoke on their personal experiences with the disease and their dedication to raising awareness. Renée Sankus, Legislative and Program Associate for the OCNA, an umbrella organization that unites the efforts of ovarian cancer grassroots activists, women's health advocates, and health care professionals, advised that the Alliance's mission was to increase public and professional understanding of ovarian cancer and to lobby for increased funding for research into more effective diagnostic tools and treatment options. FCCC staff members, Mary B. Daly, M.D., Ph.D., Director of the Margaret Dyson Family Risk Assessment Program, Paul F. Engstrom, M.D., Senior Vice President of the Division of Population Science and Principal Investigator of the Ovarian Cancer Prevention Program, and Carol Cherry, RNC, BSN, OCN, Project Manager of the Ovarian Cancer Consortium for Research and Surveillance described the various ovarian cancer prevention programs ongoing at FCCC and thanked those in attendance for their support and participation. The reception provided an opportunity for interaction among program participants and a chance for them to meet the Family Risk Assessment Program staff.

Guests admiring quilters' creativity

Left to right:
Virginia Tokarski, Laura Manning, Maileen Zimmerman

Sonia Breccia

When Life Gives You Scraps, Make a Quilt!

Many crafty quilters have volunteered to make a Fox Chase Ovarian Cancer Awareness Quilt. Brainstorming a design is underway. Stay tuned for more details! For more information, call Carol Cherry at 1-800-325-4145.

Ovarian Family Registry Update

Understanding the factors that contribute to ovarian cancer is an important challenge in molecular genetic research. A major goal of the Ovarian Cancer Consortium for Research and Surveillance (OCCRS) is to collect biospecimens to support much-needed research. To date, the effort has been successful in collecting blood from 215 ovarian cancer patients and 352 women at risk. These women represent 273 families in the US and Canada affected with ovarian cancer. Collecting tumor tissue samples is a slower process but as of March 1, 2001, 40 samples have been received.

In support of the OCCRS, Dr. Andrew K. Godwin has established a laboratory to help process, store, and distribute biospecimens (e.g., serum, platelets, DNA, lymphocytes, tumor and normal tissue) obtained from individuals participating in our program. To date, many studies are being conducted that are utilizing this valuable resource. A sample of the studies are listed below:

Identification of potential biomarkers of impending cancer.

A subset of the women in the OCCRS have chosen prophylactic oophorectomy (removal of healthy ovaries by surgery) to help prevent ovarian cancer and have donated their ovaries for research. In the past year Dr. Godwin's lab has collected ovarian tissue from 37 women, ages ranging from 36 to 79 years. Samples have been collected from 27 different hospitals throughout the United States. Tissue sections of all of the ovaries are being evaluated for evidence of pre-cancerous changes. Cells are being grown from these tissues to study the potential benefit of new chemopreventive agents (i.e., drugs that may prevent the occurrence of disease).

Identification of DNA markers that are associated with an increased risk of ovarian cancer.

DNA is isolated from the white blood cells of individuals who have contributed blood to the OCCRS. The DNA is being evaluated for small changes in the genes commonly referred to as polymorphisms. The frequency (i.e., how often the specific change is observed) of the polymorphisms in women with cancer is being compared with those in women at the same ages who have not developed disease. If a polymorphism in a specific gene is found more often in women with ovarian cancer as compared to disease-free individuals, scientists will be able to begin to identify individuals who may be at an increased risk of developing ovarian cancer.

These studies will provide important insights regarding genetic mechanisms associated with ovarian cancer as well as new approaches for earlier diagnosis and prevention. Please keep us advised of any changes in your health, the health of family members and any plans to undergo preventive or cancer surgery. Your support of the OCCRS is a vital link in the quest to find a cure for ovarian cancer.

Quality of Life after Prophylactic Oophorectomy

Ovarian cancer survivors tell us they want more research into quality of life issues after surgery to remove their ovaries, also known as oophorectomy. This study will help us learn how this surgery affects issues regarding menopausal symptoms, self-concept and sexual functioning. If you are considering surgery to help prevent ovarian cancer, or if you have had this surgery in the past, you may be eligible to participate. Study participants will be mailed a series of questionnaires to complete. Call Carol Cherry at 1-800-325-4145 for information.